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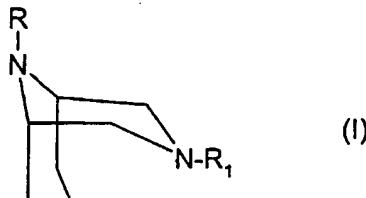
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(54) Title: 3,9-DIAZABICYCLO[3.3.1]NONANE DERIVATIVES WITH ANALGESIC ACTIVITY

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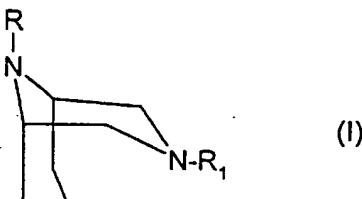
(57) Abstract: Compounds of formula (I) wherein R and R<sub>1</sub>, which are different from each other, are a straight or branched C<sub>2</sub>-C<sub>8</sub> acyl group, have analgesic activity.

3,9-DIAZABICYCLO[3.3.1]NONANE DERIVATIVES WITH ANALGESIC ACTIVITY

The present invention relates to 3,9-diazabicyclo[3.3.1]nonane derivatives, the use thereof for the preparation of medicaments with central analgesic activity and pharmaceutical compositions containing them.

In particular, the invention relates to compounds of general formula

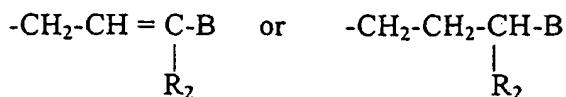
5 (I)



10 wherein

R and R<sub>1</sub>, which are different from each other, are a straight or branched C<sub>2</sub>-C<sub>8</sub> acyl group;

a group of formula



15

wherein:

B is a C<sub>6</sub>-C<sub>10</sub> aryl group, optionally substituted at the ortho-, meta- or para- positions with one or more substituents, which are the same or different, selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>2</sub> halo alkyl, C<sub>1</sub>-C<sub>3</sub> alkyl, halogens, carboxy, cyano, nitro, CONHR<sub>3</sub>; a C<sub>5</sub>-C<sub>7</sub> cycloalkyl group, a 5 or 6 membered heterocyclic aromatic group, optionally benzofused, having at least one heteroatom selected from nitrogen, oxygen, sulfur; said heterocyclic group optionally having one or more substituents as described above for the aryl group;

25 R<sub>2</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkyl or a phenyl group

optionally substituted as indicated above,

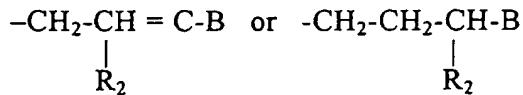
and the pharmaceutically acceptable salts thereof.

Examples of C<sub>1</sub>-C<sub>8</sub> acyl groups are acetyl, propionyl, isopropionyl, butyryl, isobutiryl, valeryl, isovaleryl, pivaloyl, caprolyl.

5 Examples of heterocyclic groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyridine, pyrimidine, pyridazine, pyrazine, benzothienyl.

10 Examples of pharmaceutically acceptable salts are those with halohydric acids, such as hydrochloric acid, hydrobromic acid; mineral acids, such as sulfuric and phosphoric acids; organic acids, such as acetic, propionic, succinic, glutaric, benzoic, salicylic acids. Any carboxylic groups can be in the salified form with alkali or alkaline-earth metal bases, such as sodium, potassium, calcium, magnesium; bases of non toxic metals; non toxic organic amines.

15 Preferred are compounds of formula (I) wherein R or R<sub>1</sub> are an acyl group as defined above or a group of formula



20 and B is a phenyl group, optionally substituted, as defined above, a naphthyl or a heterocyclic group.

Also preferred are compounds of formula (I) wherein R<sub>1</sub> is an acyl group as defined above and R is the group of formula -CH<sub>2</sub>-CH=C-B  
25  
|  
R<sub>2</sub>

3,8-Diazabicyclo[3.2.1.]octane derivatives with analgesic activity are disclosed in EP 0 746 560.

It has now been found that the compounds of formula (I) have central analgesic activity comparable to that of morphine and higher than that of 30 3,8-diazabicyclo[3.2.1.]octane, are "substantially free" from withdrawal

symptoms and less liable than morphine to induce tolerance or physical dependence after chronic treatment.

"Substantially free" herein means an activity 3 to 20 times lower than that of morphine in the mouse jumping test, after chronic administration 5 three times a day for 7 consecutive days of analgesically equipotent dosages.

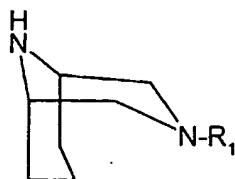
The present invention also relates to the compounds of general formula (I) as agents with central analgesic activity.

A further object of the present invention are the processes for the preparation of said compounds.

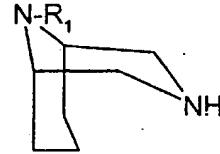
10 Still a further object of the present invention is the use of the compounds of formula (I) for the preparation of a medicament useful to induce analgesia on central nervous system in a mammal, particularly in humans, requiring such treatment.

Still a further object of the invention are pharmaceutical compositions 15 containing a therapeutically effective amount of at least one compound of formula (I) in mixture with conventional carriers and excipients.

The compounds of the invention can be prepared by reaction of intermediates of formula (IIa) or (IIb)

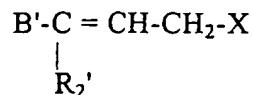


IIa



IIb

20 wherein  $\text{R}'$  is a straight or branched  $\text{C}_2\text{-C}_8$  acyl group  
with a compound of formula



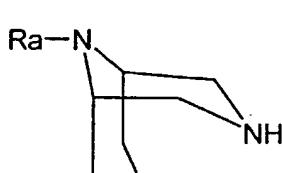
(III)

5 wherein  $\text{R}_2'$  and  $\text{B}'$  have the same meanings as  $\text{R}_2$  and  $\text{B}$  or are groups which can be transformed into  $\text{R}_2$  and  $\text{B}$ , and  $\text{X}$  is a leaving group, for example a halogen atom, mesyl, tosyl and the like.

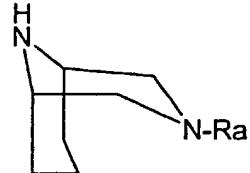
The reactions described above are carried out according to conventional techniques known to those skilled in the art. Reagents are 10 usually present in stoichiometric or slightly different ratios, depending on the reactivity of the specific reagent.

The acylation of the nitrogen at 3 or at 9 is usually carried out with acid chlorides in an inert reaction medium, such as an open or closed chain ether, a ketone, an optionally halogenated hydrocarbon, preferably in the 15 presence of a proton acceptor, such as a tertiary amine. Alternatively, the acylating agent can be a carboxylic acid anhydride.

The intermediates of formulae (IIa) and (IIb) can be obtained by acylation, according to conventional methods, of a compound of formula (IVa) or (IVb)



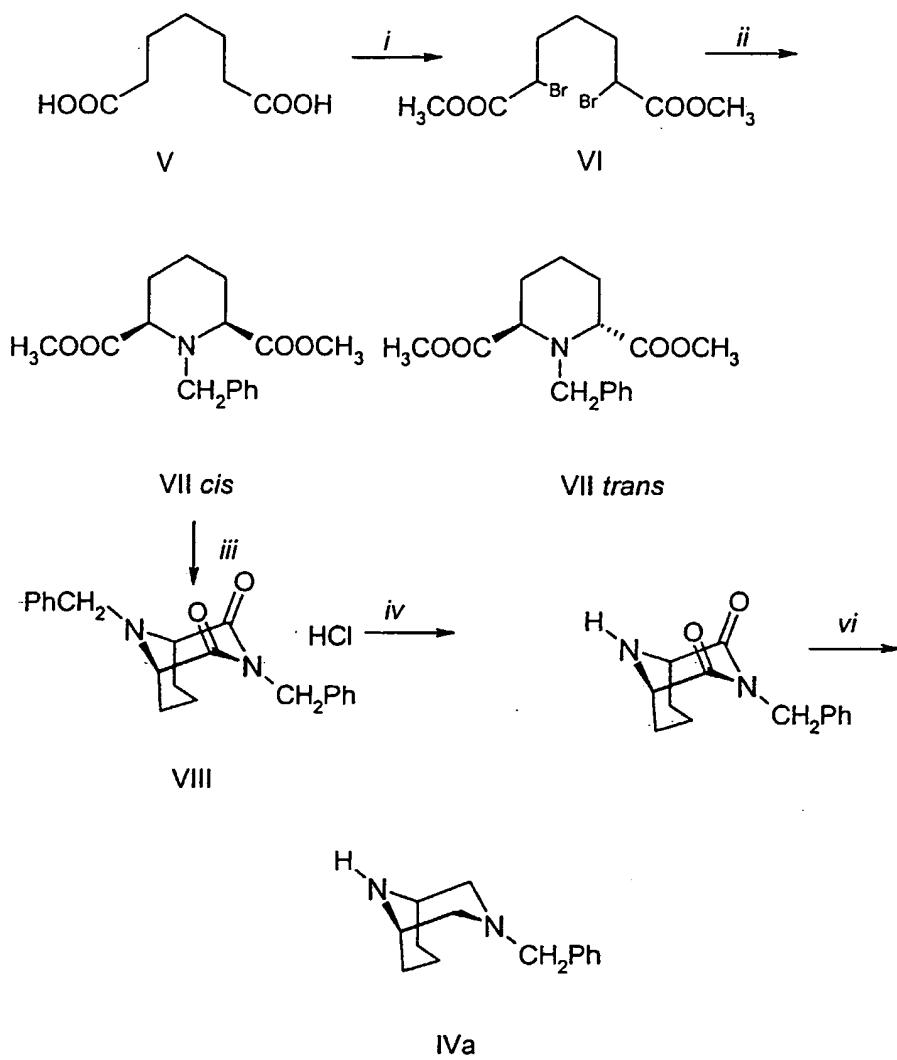
IVa



IVb

20 wherein  $\text{Ra}$  is an amino-protecting group, and subsequent removal of the protective group. Compound of formula (IVa) in which  $\text{Ra}$  is benzyl is known from Gazzetta Chimica Italiana, 1963, 226-227, and can be prepared according to the following scheme 1

Scheme 1



Meso-dimethyl- $\alpha,\alpha$ -dibromopimelate (VI) obtained by bromination of pimelic acid (V), is condensed with benzylamine in benzene under reflux to give N-benzyl-2,6-dicarbomethoxy-piperidine (VII) as *cis* and *trans* isomeric mixture, which is reacted with benzylamine in xylene under reflux for 18 hours and then, after evaporation of the solvent, for a further 4 hours a 160-170°C

The resulting compound (VIII) is recovered as hydrochloride from the

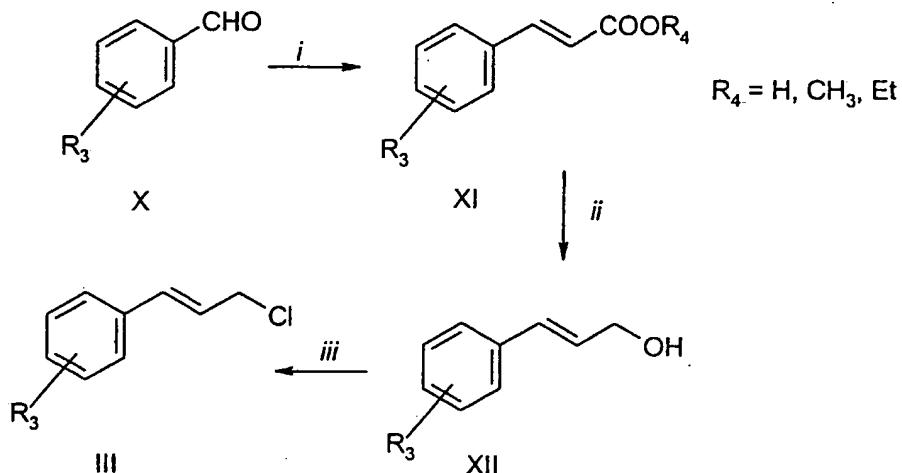
reaction product by dissolution in ethanol and precipitation with HCl, then is hydrogenolysed to give the compound (IX) which is reduced with metal hydrides such as LiAlH<sub>4</sub>, to yield compound (IVa).

Compounds (IVb) can be obtained from compounds (IVa) through  
5 thermal rearrangement, analogously to what published for the homologous diazabicyclooctanes (Tetrahedron, 1963, 9, 143-148).

Intermediates of formula (III) are known or can be prepared with known methods, for example by reducing suitable arylacryl acids or esters thereof with metal hydrides and subsequently transforming the resulting  
10 alcohol into halide, with conventional methods, according to Scheme 2 reported in the following, concerning compounds (III) in which B is optionally substituted phenyl and R<sub>2</sub> is hydrogen. Other compounds of formula (III) can be obtained with similar methods.

In Scheme, R<sub>3</sub> represents the substituents listed for the aryl group R<sub>2</sub>.

15 Scheme 2



Compounds (I) and the salts thereof with pharmaceutically acceptable acids can be advantageously used as active principles in medicaments having central analgesic activity, as well as poor liability to induce tolerance and withdrawal symptoms which are the most serious restrictions to the use of

morphine.

For the envisaged therapeutical uses, compounds (I) or the salts thereof will be formulated in a therapeutically effective amount in suitable pharmaceutical formulations according to conventional techniques and 5 excipients, such as those described in "Remington's Pharmaceutical Sciences Handbook" XVII Ed. Mack Pub., N.Y., USA.

Examples of pharmaceutical compositions are tablets, capsules, granulates, powders soluble, drops, elixirs, syrups, injectable forms, suppositories.

10 The dosages and posology will be defined by the physician depending on the severity of the disease, the conditions of the patient and any possible interactions with other medicaments.

The following examples further illustrate the invention.

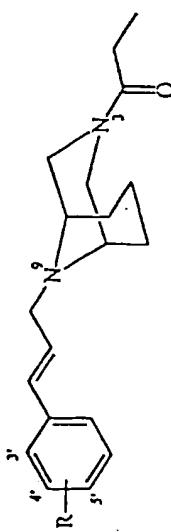
**Preparation 1**

15 3-Propionyl-3,9-diazabicyclo[3.3.1]nonane.

9-Propionyl-3,9-diazabicyclo[3.3.1.]nonane (IVa) (0.83 g, 4.56 mmol) obtained according to Gazzetta Chimica Italiana 1963, 226-227 was heated at 150°C for 2 hours. The crude product was chromatographed (silica gel) eluting with CHCl<sub>3</sub>-CH<sub>3</sub>OH/8:2.

20 The title product was recovered from the fraction with R<sub>f</sub> 0.29 as oil, b.p. 125-130°C/0.4 mmHg. IR (film, cm<sup>-1</sup>) v: 1630 (C=O), 2920 (NH); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δH: 1.16 (t, 3H), 1.50-1.70 (m, 2H), 1.80-2.20 (m, 4H), 2.35 (q, 2H), 3.15 (dd, 1H), 3.33 (br s, 2H), 3.65 (dd, 1H), 3.88 (d, 1H), 4.79 (br s, 1H exch. with D<sub>2</sub>O). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δc: 9.05 (CH<sub>3</sub>), 18.24, 26.64, 25.48, 29.49, 45.08 and 49.22 (CH<sub>2</sub>x6), 46.53 and 46.61 (CHx2), 172.58 (C=O) from DEFT (135°C) and HETCOR.

## EXAMPLES 1-16

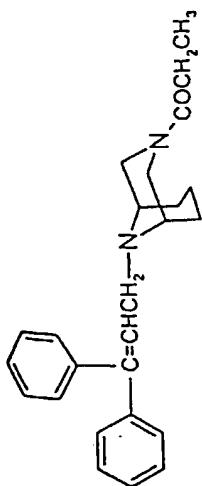


Ex.	R	Yield %	m.p. °C	Formula (Analysis) <sup>a</sup>	IR C ν cm <sup>-1</sup>	<sup>1</sup> H-NMR δ ppm
8	H	36	oil	C <sub>19</sub> H <sub>26</sub> N <sub>2</sub> O (C <sub>11</sub> H <sub>14</sub> N)	1525, 1635	1.19 (t, 3H); 1.46-1.66 (m, 2H); 1.72-2.20 (m, 4H); 2.21-2.40 (m, 2H); 2.92 (br s, 2H); 3.18 (dd, 1H); 3.50-3.80 (m, 4H); 4.40 (d, 1H); 6.20-6.30 (dt, 1H); 6.60 (d, 1H); 7.20-7.40 (m, 5H).
9	4'-NO <sub>2</sub>	22	oil	C <sub>19</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub> (C <sub>11</sub> H <sub>13</sub> N)	1360, 1515	1.19 (t, 3H); 1.47-1.70 (m, 2H); 1.72-2.20 (m, 4H); 2.21-2.40 (m, 2H); 3.01 (br s, 2H); 3.50-3.70 (m, 5H); 4.37 (d, 1H); 6.30-6.40 (dt, 1H); 6.60 (d, 1H); 7.50 (d, 1H); 8.20 (d, 2H).
10	3'-Cl	27	oil	C <sub>19</sub> H <sub>25</sub> ClN <sub>2</sub> O (C <sub>11</sub> H <sub>14</sub> ClN)	1630	1.17 (t, 3H); 1.40-1.60 (m, 2H); 1.70-2.20 (m, 4H); 2.30-2.50 (m, 2H); 2.98 (br s, 2H); 3.10 (dd, 1H); 3.40-3.60 (m, 4H); 4.40 (d, 1H); 6.20-6.40 (dt, 1H); 6.45 (d, 1H); 7.01-7.40 (m, 4H).
11	3',4'-Cl <sub>2</sub>	36	oil	C <sub>19</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>2</sub> O (C <sub>11</sub> H <sub>13</sub> Cl <sub>2</sub> N)	1635	1.17 (t, 3H); 1.40-1.60 (m, 2H); 1.70-2.10 (m, 4H); 2.20-2.40 (m, 2H); 2.89 (br s, 2H); 3.40-3.60 (m, 5H); 4.20 (d, 1H); 6.20-6.30 (dt, 1H); 6.40 (d, 1H); 7.10-7.20 (m, 1H); 7.30-7.50 (m, 2H).
12	3'-NO <sub>2</sub> , 4'-Cl	60	oil	C <sub>19</sub> H <sub>24</sub> ClN <sub>3</sub> O <sub>3</sub> (C <sub>11</sub> H <sub>14</sub> ClN <sub>2</sub> O <sub>3</sub> )	1330, 1520	1.19 (t, 3H); 1.42-1.62 (m, 2H); 1.70-2.20 (m, 4H); 2.20-2.40 (m, 2H); 2.92 (br s, 2H); 3.15 (dd, 1H); 3.40-3.60 (m, 4H); 4.40 (d, 1H); 6.20-6.40 (dt, 1H); 6.52 (d, 1H); 7.40-7.60 (m, 2H); 7.80 (s, 1H).
13	2'-NO <sub>2</sub> , 5'-Cl	25	130 (dec) <sup>a</sup>	C <sub>19</sub> H <sub>24</sub> ClN <sub>3</sub> O <sub>3</sub> ·HCl (C <sub>11</sub> H <sub>14</sub> ClN <sub>2</sub> O <sub>3</sub> ·HCl)	1340, 1520	1.17 (t, 3H); 1.42-1.65 (m, 2H); 1.70-2.20 (m, 4H); 2.37 (q, 2H); 2.93 (br s, 2H); 3.12 (dd, 1H); 3.50-3.75 (m, 4H); 4.40 (d, 1H); 6.15-6.30 (dt, 1H); 7.01 (d, 1H); 7.30 (dd, 1H); 7.56 (d, 1H); 7.92 (d, 1H).
14	2'-Cl, 5'-NO <sub>2</sub>	30	245 <sup>a</sup>	C <sub>19</sub> H <sub>24</sub> ClN <sub>3</sub> O <sub>3</sub> ·HCl (C <sub>11</sub> H <sub>14</sub> ClN <sub>2</sub> O <sub>3</sub> ·HCl)	1340, 1520 1560, 1635	1.17 (t, 3H); 1.48-1.68 (m, 2H); 1.72-2.18 (m, 4H); 2.34 (dq, 2H); 2.93 (br s, 2H); 3.15 (dd, 1H); 3.42-3.78 (m, 4H); 4.40 (d, 1H); 6.30-6.50 (dt, 1H); 7.01 (d, 1H); 7.65 (d, 1H); 8.05 (dd, 1H); 8.42 (d, 1H).

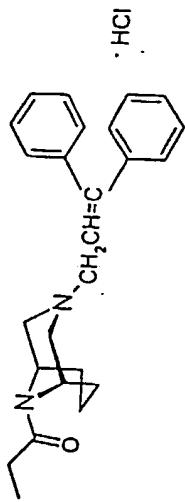


Ex.	R	Yield %	m.p. °C	Formula (Analysis) <sup>b</sup>	IR <sup>C</sup> ν cm <sup>-1</sup>	<sup>1</sup> H-NMR δ ppm
1	H	72	oil	$\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}$ ( $\text{C},\text{H},\text{N}$ )	1635	1.16 (t, 3H); 1.40-1.60 (m, 1H); 1.70-1.95 (m, 4H); 2.20-2.40 (m, 4H); 2.70-3.15 (m, 5H); 3.88 (br s, 1H); 4.70 (br, s, 1H); 6.20-6.40 (dt, 1H); 6.50 (d, 1H); 7.20- 7.40 (m, 5H).
2	4'-NO <sub>2</sub>	34	oil	$\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_3$ ( $\text{C},\text{H},\text{N}$ )	1350-1510 1620	1.17 (t, 3H); 1.50-1.70 (m, 1H); 1.70-1.92 (m, 4H); 2.20-2.40 (m, 4H); 2.65-3.20 (m, 5H); 3.95 (brs, 1H); 4.73 (br, s, 1H); 6.40-6.60 (m, 2H); 7.55 (d, 2H); 8.20 (d, 2H); 1.18 (t, 3H); 1.40-1.60 (m, 1H); 1.70-1.93 (m, 4H); 2.20- 2.40 (m, 4H); 2.80-3.10 (m, 5H); 3.88 (br s, 1H); 4.68 (br, s, 1H); 6.10-6.30 (dt, 1H); 6.50 (d, 1H); 7.20-7.30 (m, 4H); 1.11 (t, 3H); 1.42-1.63 (m, 1H); 1.70-1.90 (m, 4H); 2.20- 2.40 (m, 4H); 2.80-3.10 (m, 5H); 4.05 (br s, 1H); 4.65 (br, s, 1H); 6.10-6.30 (dt, 1H); 6.40 (d, 1H); 7.10-7.50 (m, 3H); 1.15 (t, 3H); 1.50-1.70 (m, 1H); 1.75-1.95 (m, 4H); 2.22- 2.42 (m, 4H); 2.85-3.25 (m, 5H); 3.89 (br s, 1H); 4.73 (br, s, 1H); 6.15-6.24 (dt, 1H); 6.40-6.50 (m, 2H); 7.40 (br s, 2H); 7.80 (s, 1H).
3	3'-Cl	64	oil	$\text{C}_{19}\text{H}_{25}\text{ClN}_2\text{O}$ ( $\text{C},\text{H},\text{N}$ )	1640	
4	3'4'-Cl <sub>2</sub>	72	oil	$\text{C}_{19}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}$ ( $\text{C},\text{H},\text{N}$ )	1635	
5	3'-NO <sub>2</sub> , 4'-Cl	76	oil	$\text{C}_{19}\text{H}_{24}\text{ClN}_3\text{O}_3$ ( $\text{C},\text{H},\text{N}$ )	1335, 1524 1630	
6	2'-NO <sub>2</sub> , 5'-Cl	25	130-134 <sup>a</sup>	$\text{C}_{19}\text{H}_{24}\text{ClN}_3\text{O}_3\text{HC}$ ( $\text{C},\text{H},\text{N}$ )	1340, 1520 1630	1.17 (t, 3H); 1.50-1.70 (m, 1H); 1.70-1.95 (m, 4H); 2.23- 2.45 (m, 4H); 2.65-3.20 (m, 5H); 3.90 (br s, 1H); 4.72 (br, s, 1H); 6.17-6.24 (dt, 1H); 7.05 (d, 1H); 7.30 (dd, 1H); 7.56 (d, 1H); 7.92 (d, 1H).
7	2'-Cl, 5'-NO <sub>2</sub>	31	208-210 <sup>a</sup>	$\text{C}_{19}\text{H}_{24}\text{ClN}_3\text{O}_3\text{HC}$ ( $\text{C},\text{H},\text{N}$ )	1345, 1525 1640	1.17 (t, 3H); 1.50-1.70 (m, 1H); 1.70-1.95 (m, 4H); 2.25- 2.45 (m, 4H); 2.80-3.20 (m, 5H); 3.95 (br s, 1H); 4.72 (br, s, 1H); 6.34-6.48 (dt, 1H); 6.95 (d, 1H); 7.53 (d, 1H); 8.03 (dd, 1H); 8.40 (d, 1H).

10



Ex.	R	Yield %	m.p. °C	Formula (Analysis <sup>b</sup> )	IR <sup>c</sup> ν cm <sup>-1</sup>	<sup>1</sup> H-NMR δ ppm
15		54	102-105 <sup>a</sup>	C <sub>25</sub> H <sub>30</sub> N <sub>2</sub> ·HCl (C <sub>12</sub> H <sub>15</sub> N)	1650	1.17 (t, 3H); 1.40-1.60 (m, 2H); 1.70-2.10 (m, 4H); 2.20-2.40 (m, 2H); 2.89 (br s, 2H); 3.40-3.60 (m, 4H); 4.26 (d, 2H); 6.18 (t, 1H); 7.00-7.50 (m, 10H).



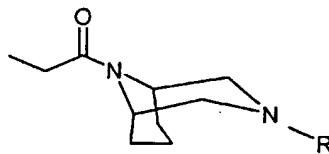
Ex.	Yield %	m.p. °C
16	59	55-57

**General procedure**

A mixture of compounds (IVa) or (IVb) (2.30 mmol), the desired cinnamyl halide (2.30 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.30 mmol) in acetone or butanone (13.5 ml) was refluxed for 4-12 hours. Inorganic salts were filtered off, the  
5 filtrate was evaporated and the oily residue was purified by flash chromatography (eluent CH<sub>2</sub>Cl<sub>3</sub>: acetone /9:1) to give the compounds reported in the following tables as oils or as hydrochlorides.

## Examples 17-30

According to similar procedures, the following compounds were prepared:



Ex.	R	m.p.
17		110°
18		141°
19		125-30°
20		130-5°
21		oil
22		oil
23		153°



Ex.	R	m.p.
24		138°
25		143°
26		128-32°
27		134-38°
28		oil
29		oil
30		123-6°

## Example 31

## Pharmacological activity

Binding studies on the opioid receptors were carried out on mouse brain homogenates, in the presence of [<sup>3</sup>H]-DAMGO for  $\mu$  [<sup>3</sup>H]-  
 5 DELTORPHINE (II) for  $\delta$ . [<sup>3</sup>H]-U69, 593 was used on guinea pigs homogenates to evaluate the  $\kappa$  binding. Morphine was used as the reference compound.

The results are reported in the following tables.

Table 1

10 Binding affinity to  $\mu$ ,  $\delta$  and  $\kappa$  receptors

Compound of Ex.	Binding affinities (Ki nM) <sup>a</sup>		
	$\mu$	$\delta$	$\kappa$
1	29±2.0	12000±1152	>50000
8	13±1.5	1750±144	2000±180

<sup>a</sup>Each value is the mean ± SEM of independent tests, each of them carried out in triplicate (n=3).

Table 2

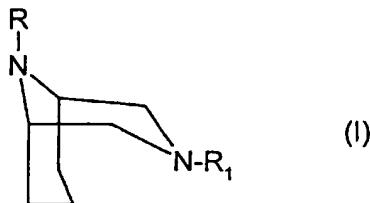
15 Inhibition constants towards  $\mu$  opioid receptors

Compound of Ex.	[ <sup>3</sup> H]-DAMGO (Ki nM) <sup>a</sup>
2	29.0
3	70.0
4	48.33
8	13.0
9	7.66
10	8.66
11	5.83
12	18.0
13	6.0
14	6.0

<sup>a</sup>Values of Ki were calculated based on K<sub>d</sub> values of 1nM for [<sup>3</sup>H]-DAMGO. Values are the mean from two experiments.

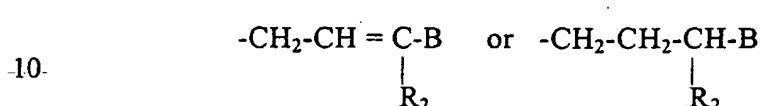
CLAIMS

## 1. Compounds of formula 1:



5 wherein

R and R<sub>1</sub>, which are different from each other, are a straight or branched C<sub>2</sub>-C<sub>8</sub> acyl group;  
a group of formula



wherein:

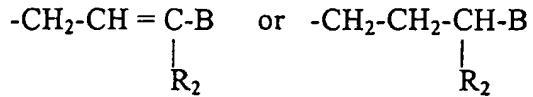
B is a C<sub>6</sub>-C<sub>10</sub> aryl group, optionally substituted at the ortho-, meta- or para-positions with one or more substituents, which are the same or different,  
15 selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>2</sub> halo alkyl, C<sub>1</sub>-C<sub>3</sub> alkyl, halogens, carboxy, cyano, nitro, CONHR<sub>3</sub>; a C<sub>5</sub>-C<sub>7</sub> cycloalkyl group, a 5 or 6 membered heterocyclic aromatic group, optionally benzofused, having at least one heteroatom selected from nitrogen, oxygen, sulfur; said heterocyclic group optionally having one or more substituents as described  
20 above for the aryl group;

R<sub>2</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkyl or a phenyl group optionally substituted as indicated above;

and the pharmaceutically acceptable salts thereof.

2. Compounds as claimed in claim 1 wherein R or R<sub>1</sub> are an acyl group as

defined in claim 1 or a group of formula



5 and B is an optionally substituted phenyl group as defined in claim 1, or a naphthyl group or a benzofused heterocyclic group.

3. Compounds as claimed in claim 1 wherein R<sub>1</sub> is an acyl group as defined in claim 1 and R is the group of formula



10

4. Compounds as claimed in claims 1-3 as central analgesic agents.

5. The use of the compounds of claims 1-3 for the preparation of analgesic medicaments.

## INTERNATIONAL SEARCH REPORT

ional Application No  
PCT/EP 01/01541

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D471/08 A61K31/4995 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	PINNA, G. A. ET AL: "Synthesis, modeling, and m-opioid receptor affinity of N-3(9)-arylpropenyl-N-9(3)-propionyl-3,9-diazabicyclo'3.3.1!nonanes" IL FARMACO, vol. 55, no. 8, 2000, pages 553-562, XP.001000530 The whole document; in particular compounds 1a-g and 2a-g. --	1-5
Y	US 5-672-601 A (CIGNARELLA GIORGIO) 30 September 1997 (1997-09-30) cited in the application Claims 1-2; column 2, lines 44-48. -- --/--	1-5

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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Date of the actual completion of the international search

Date of mailing of the international search report

8 June 2001

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## INTERNATIONAL SEARCH REPORT

stional Application No  
PCT/EP 01/01541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BARLOCCO, D. ET AL.: "Synthesis and mu-opioid receptor affinity pf a new series of nitro substituted 3,8-diazabicyclo(3.2.1)octane derivatives" IL FARMACO, vol. 53, 1998, pages 557-562, XP001000529 Abstract; compounds 1a-j and 2a-i. ---	1-5
Y	BALLABIO M ET AL: "2,2,6- and 2,3,5-Trimethylpiperazines as Monocyclic Analogues of the mu-Opioid Agonist 3,8-Diazabicyclo[3.2.1]octanes: Synthesis, Modeling, and Activity" TETRAHEDRON, vol. 53, no. 4, 27 January 1997 (1997-01-27), pages 1481-1490, XP004105235 ISSN: 0040-4020 Page 1481. ---	1-5
Y	BARLOCCO, D. ET AL.: "Computer-aided structure-affinity relationship ..." J. COMPUTER-AIDED MOLECULAR DESIGN, vol. 7, 1993, pages 557-571, XP001000932 The whole document; in particular pages 561, 571, and figures 5 and 6. ---	1-5
A	CIGNARELLA, G. ET AL.: "Trasposizione intramolecolare acilica nella serie del 3,9-diazabiciclo(3.3.1)nonano" GAZZ. CHIM. ITAL., vol. 93, 1963, pages 320-325, XP001000561 Compounds III-IX. -----	1-5

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

National Application No

PCT/EP 01/01541

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		AU	1808595 A	11-09-1995
		EP	0746560 A	11-12-1996
		WO	9523152 A	31-08-1995